Preventing diabetes — applying pathophysiological and epidemiological evidence

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This is a review of research carried out in Japanese Americans that points towards possible approaches to prevention of type 2 diabetes mellitus. The natural history of type 2 diabetes usually includes both insulin resistance and β-cell dysfunction. Insulin secretion may compensate for insulin resistance. Alternatively, enhanced insulin sensitivity may mask an insulin secretory defect. Epidemiological data support the view that in the vast majority of cases of type 2 diabetes, insulin resistance is essential to the pathogenesis of hyperglycemia. Increased diabetes prevalence as ethnic groups migrate to more urban or westernized regions has been attributed to increased occurrence of insulin resistance. Research among Japanese Americans in Seattle, Washington, showed a higher prevalence of type 2 diabetes than in Japan, which suggested that factors associated with 'westernization' might be playing a role in bringing out underlying susceptibility to diabetes. Our research has shown that these impressions were correct and that the abnormalities that characterize the metabolic syndrome play a significant role. Due to increased intra-abdominal fat deposition, Japanese Americans were likely to be 'metabolically obese' despite relatively normal BMI. A diet higher in animal fat and lower levels of physical activity were risk factors leading to increased intra-abdominal fat deposition, insulin resistance, and diabetes. Information from epidemiological studies such as these may be used to determine whether diabetes may be prevented through changes in lifestyle or application of specific therapies targeted towards identified metabolic abnormalities.

β-Cell dysfunction: Insulin resistance: Metabolic obesity: Westernization

World-wide diabetes prevalence rates suggest that increasing westernization and urbanization are associated with higher rates of diabetes (King *et al.* 1993, 1998). There are many examples of this. One example are the Japanese in the United States. In the early 1980s the prevalence of diabetes among Nisei (second-generation Japanese Americans) in Seattle was four times the published rates from Tokyo, under identical diagnostic criteria — 20 % in men and 16 % in women in Seattle compared to 5 % and 4 % in men and women, respectively in Tokyo (Fujimoto *et al.* 1994*b*). This observation strongly suggested that the exposure of Japanese to an American life-style brought out an inherent tendency to develop diabetes. The question remained as to what factors were important and how this came about. This review summarizes several key findings of our research that address this question.

The major metabolic defects in type 2 diabetes

The diagnostic hallmark of diabetes is hyperglycemia, demonstrated in either the fasting state or following glucose. Although there is debate about whether the fasting plasma glucose or the oral glucose tolerance test (OGTT) are better for the diagnosis of diabetes, there is general agreement that the pathogenesis of hyperglycemia can be attributed to abnormalities in three areas (Kahn & Porte, 1997). These are the action of insulin upon peripheral tissues such as muscle and fat, the ability of the pancreatic islet β-cells to produce and secrete insulin, and the regulation of hepatic glucose production. With diabetes there is insulin resistance, pancreatic islet β-cell dysfunction, and hepatic glucose over-production.

The natural history of type 2 diabetes is characterized by

Abbreviations: BMI, body mass index; CT, computed tomography; OGTT, oral glucose tolerance test.

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transition from normal glucose tolerance to an intermediate state of metabolic abnormality that has been called 'impaired glucose homeostasis' (The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 1997). Included in impaired glucose homeostasis are two conditions, impaired fasting glucose and impaired glucose tolerance. The former is diagnosed by a fasting plasma glucose level from 6·1 to <7·0 mM while the latter is diagnosed by a 2 h plasma glucose level from 7·8 to <11·1 mM during a 75 g oral glucose tolerance test. Diabetes is diagnosed by a fasting plasma glucose ≥7·0 mM and/or a 2 h plasma glucose ≥11·1 mM. Both impaired glucose homeostasis and diabetes are accompanied by varying degrees of abnormalities in insulin action, insulin secretion, and hepatic glucose production.

Insulin resistance, obesity, and body fat distribution

To learn more about why diabetes was more prevalent in Japanese Americans than in native Japanese in Tokyo, Seattle Nisei and Tokyo Japanese men with diabetes who were matched by age were compared (Fujimoto *et al.* 1989). During an oral glucose tolerance test, both groups were similarly hyperglycemic. However, the Seattle men had significantly higher fasting insulin levels as well as insulin levels during a 75 g OGTT. These observations are consistent with greater insulin resistance among the Seattle men. In addition, the Seattle men had significantly higher mean body mass index (BMI).

It is known that diabetes prevalence is related to obesity, although the relationship differs by race and ethnicity. It is also known that weight loss improves insulin sensitivity. Thus the greater insulin resistance in Seattle men was consistent with their being heavier than the Tokyo men. In turn, the greater insulin resistance in Seattle men could be responsible for the greater prevalence of diabetes in Nisei. If the greater degree of insulin resistance in Seattle men was due to their greater BMI, adjustment for BMI should result in the insulin levels no longer being significantly different. However, fasting insulin remained significantly different between the Seattle and Tokyo men following adjustment for BMI. This suggested that BMI differences could not completely account for the greater insulin resistance in the Seattle men.

It is clear that the pattern of body fat distribution is significantly related to metabolic disease (Vague, 1956). The android or abdominal pattern consists of greater amounts of fat on and in the trunk while the gynoid or lower body pattern is characterized by more peripheral fat, particularly around the hips and thighs. The former pattern is associated with greater metabolic risk. Hence this type of body fat pattern represents 'metabolic obesity'. Moreover, the android pattern that is associated with intra-abdominal or visceral fat is at the greatest risk for metabolic disease (Matsuzawa *et al.* 1992). Intra-abdominal fat may be measured by using either computed tomography (CT) or magnetic resonance imaging.

When adipose variables were compared in Nisei men with and without type 2 diabetes, intra-abdominal fat as measured by CT was the only adipose measurement that was associated with diabetes (Shuman *et al.* 1986). The other adipose variables included BMI, skinfolds, and circumferences. Men with low amounts of intra-abdominal fat tended to have normal glucose tolerance while those with high amounts tended to be diabetic.

Subsequent research showed that the insulin sensitivity index of Bergman, Si, was significantly correlated with intra-abdominal fat (Fujimoto *et al.* 1994*a*). Furthermore, intra-abdominal fat correlated better than Si did with a variety of metabolic variables that are associated with the insulin resistance syndrome. Prospectively, intra-abdominal fat was also shown to be a risk factor for the development of diabetes (Bergstrom *et al.* 1990*a*).

β-Cell lesions of diabetes

Insulin resistance, however, is insufficient to cause hyperglycemia. This is exemplified by a study of insulin sensitivity in persons with perfectly normal glucose tolerance (Bergman, 1989). Whereas white males were very insulin sensitive, women in the third trimester of pregnancy were extremely resistant to insulin. A study of the relationship between insulin secretion and insulin action showed that in persons with normal glucose tolerance, insulin secretion can adequately compensate for insulin resistance. This suggests that for diabetes to develop in persons who are insulin resistant, β-cell function must be impaired.

It is clear that among persons with type 2 diabetes are individuals who have low amounts of intra-abdominal fat and who are thus presumably not very insulin resistant. Such individuals are diabetic because they have a more profound β-cell defect than diabetic persons with large amounts of intra-abdominal fat.

The β-cell abnormalities associated with diabetes fall into two main categories, altered stimulus-secretion coupling of glucose as an insulin secretagogue and abnormal processing of secretory proteins. As an example of the former, during an oral glucose tolerance test, individuals with impaired glucose tolerance and with diabetes have delayed secretion of insulin (Bergstrom *et al.* 1990*b*). This delay was seen at baseline in non-diabetic Japanese Americans who subsequently developed diabetes during a 5-year follow-up period (Chen *et al.* 1995). Thus abnormal stimulus-secretion coupling was present in persons who were prediabetic.

An example of abnormal secretory protein processing is demonstrated by higher proinsulin levels, expressed both as concentration of proinsulin and as proinsulin as a percentage of total immunoreactive insulin, in persons with diabetes compared to those with normal glucose tolerance (Kahn *et al.* 1995). Moreover, at baseline while still non-diabetic, those Japanese Americans who subsequently were found to have diabetes had higher fasting plasma levels of proinsulin than those who remained non-diabetic. In other words, higher proinsulin was a marker for prediabetes.

Interaction of insulin resistance and β-cell dysfunction in the pathogenesis of type 2 diabetes

Both genetic and environmental factors interact to cause insulin resistance. In response to insulin resistance, the

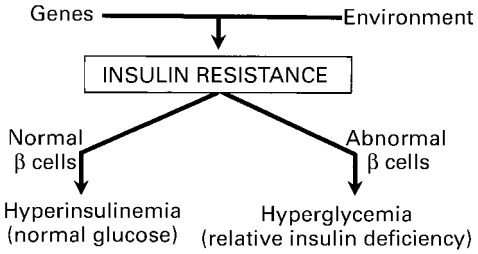

Fig. 1. Insulin resistance as the primary abnormality — normoglycemia with hyperinsulinemia or hyperglycemia with relative insulin deficiency.

normal β-cell hypersecretes insulin, resulting in hyperinsulinemia. In contrast, the abnormal β-cell cannot fully compensate, resulting in relative insulin deficiency and hyperglycemia (Fig. 1).

Genes and environment also interact to cause impaired β-cell function. As long as insulin sensitivity is retained, however, glucose tolerance remains normal despite hypoinsulinemia. If insulin resistance develops, hyperglycemia ensues because of insulin deficiency (Fig. 2).

The contributions of intra-abdominal fat, insulin resistance, and impaired β-cell function to the development of diabetes were examined in a group of 137 non-diabetic Nisei men followed for 5 years (Chen *et al.* 1995). Thirteen men had developed diabetes at 2.5 years and ten had developed it at 5 years of follow-up. At baseline, the first group had significantly increased intra-abdominal fat, elevated fasting plasma C-peptide, and lower insulin secretion at 30 min following oral glucose. The second group also had significantly lower insulin secretion at 30 min following oral glucose at baseline, but no significant difference in intra-abdominal fat or fasting C-peptide levels. When this group developed diabetes at 5 years, however, an increase of intra-abdominal fat was found superimposed upon the pre-existing lower insulin response. Thus both insulin resistance and impaired β-cell function contribute to the development of type 2 diabetes in Japanese Americans, and impaired β-cell function may be present earlier than visceral adiposity in some who subsequently develop diabetes.

Life-style and diabetes

Both genetic and life-style factors are important in the etiology of diabetes. Family history of diabetes is often used to indicate genetic risk while physical activity (energy expenditure) and dietary composition are used to assess life-style. Among dietary factors, animal fat (saturated fat) intake has been implicated as an important risk factor for diabetes.

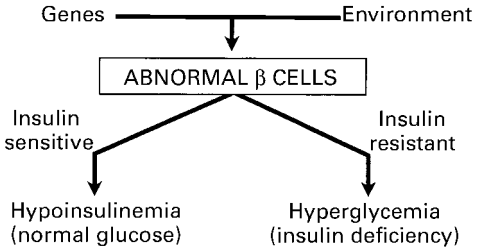

Fig. 2. Pancreatic islet β-cell as the primary abnormality — normoglycemia with hypoinsulinemia or hyperglycemia with insulin deficiency.

Persons with impaired glucose tolerance are at a greatly increased risk of subsequently developing diabetes. They therefore represent an important group for determining antecedent risk factors for diabetes. Nisei men who had impaired glucose tolerance were followed for 5 years, at which time 75 g oral glucose tolerance tests were done and 2 h plasma glucose levels measured. The 5-year glucose level was examined in terms of baseline mean energy expenditure and animal fat intake and family history of diabetes. This analysis showed that glucose levels at 5 years were significantly increased in men with a family history of diabetes who were exercising less or eating more animal fat than at baseline. Thus physical activity and diet are indeed important risk factors and these interact with genetic factors (Leonetti *et al.* 1996).

Diabetes risk in Japanese-American women

Baseline characteristics of Japanese-American women by follow-up glucose tolerance status showed that those who go on to develop diabetes were significantly older and had significantly greater amounts of intra-abdominal fat. The difference in intra-abdominal fat was greatly attenuated when adjusted for age.

Sansei (third generation Japanese-American) have lower diabetes rates than do Nisei. Sansei in our study cohort are about 20 years younger than the Nisei so the lower diabetes rates are expected. Nonetheless, there are age-related gender differences that are quite striking. For example, Sansei women have much lower cumulative incidence rates for diabetes than do Sansei men. On the other hand, Nisei women have similar or higher cumulative incidence rates for diabetes as Nisei men. Thus the disparity between Nisei and Sansei is much greater for women than men.

Since the distribution of body fat is a risk factor for diabetes, we looked at this in women. By CT scan, Nisei women had more intra-abdominal and thoracic subcutaneous fat and less thigh subcutaneous fat than did Sansei women. The result is a more android pattern of body fat distribution in Nisei women.

Several variables related to diabetes — glucose, c-peptide, intra-abdominal fat, and BMI — were examined by age in Japanese-American women. For all of these except BMI, there was a significant increase with age, consistent with a deteriorating glucose tolerance, increasing insulin resistance, and more visceral adiposity. In addition, however, there was a particularly notable increase in intra-abdominal fat between the age groups 40–49 years and 50–59 years. Since the average age of menopause is 51 years, these results strongly suggest that Japanese-American women may be relatively protected against diabetes until after they pass through the menopause, and that the increased risk seen following the menopause may be due to increased visceral fat and increased insulin resistance.

Implications for Japan

Studies in Japanese Americans therefore strongly suggest that the superimposition of 'metabolic obesity' with concomitant insulin resistance has brought out an underlying decreased β-cell reserve, resulting in hyperglycemia and diabetes. If this sequence is correct, we may anticipate diabetes rates in Japan to increase as many western lifestyle customs are adopted.

Recent diabetes prevalence data from Japan indicate diabetes rates to be much higher than were present in the early 1980s when we began our research (Fujimoto *et al.* 1994*b*). Based upon these latest data, it is probably safe to estimate diabetes prevalence to be at least 10 % in Japan in 1990. Moreover, secular trends of nutrient intake in Japan from 1955 to 1995 clearly show an increase in national consumption of animal protein and animal fat (Kitagawa *et al.* 1998). Thus the question is when will diabetes prevalence reach the 20 % rate found in Seattle Nisei in 1983?

Conclusions

Epidemiological studies such as ours show associations that suggest cause and effect. To prove the latter, however, clinical trials are required. We can use the information from epidemiological studies to develop interventions to prevent diabetes.

Although there is no way to modify genetic factors, life-style can be altered. These life-style changes — diet and exercise — can be applied broadly or may be directed towards individuals who are judged to be at increased risk for diabetes as ascertained by information such as family history of diabetes or physical findings such as central obesity. Metabolic profiling may become a tool in the future to identify persons who are at increased metabolic risk for diabetes because of insulin resistance or diminished β-cell function. This information may be useful in directing therapies that appropriately address the identified metabolic abnormalities.

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